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Total Synthesis of Amphidinolide K, a Macrolide That Stabilizes F-Actin

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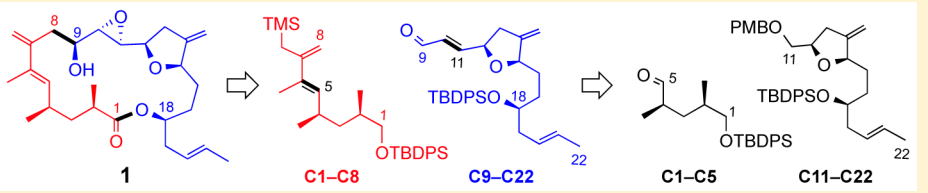
Supporting Information



ABSTRACT: The total synthesis of (−)-amphidinolide K (**1**) based on asymmetric addition of allylsilane **C1−C8** to enal **C9−C22** is reported. The 1,9,18-tris-*O*-TBDPS ether was converted into the desired 9,18-dihydroxy acid. Its macrolactonization was accomplished by the Shiina method. Compound **1** together with some of its stereoisomers and analogues were subjected to evaluation of the possible disruption of the α,β-tubulin−microtubule and/or G-actin−F-actin equilibria. Compound **1** behaves as a stabilizer of actin filaments (F-actin) in vitro.

INTRODUCTION

Amphidinolide K is a cytotoxic macrolide that was isolated from a marine *Amphidinium* dinoflagellate by Kobayashi et al.[1] Its approximate structure was deduced from only 0.3 mg of sample. Williams and Meyer, who achieved the synthesis of several of its stereoisomers, including the enantiomer of amphidinolide K, concluded that the absolute configuration of the natural product is that depicted here as **1**.[2] A total synthesis of **1** was recently published,[3] and some fragments have also been described.[4,5] Here, we report the second total synthesis of the natural enantiomer of amphidinolide K (**1**), a highly modified polypropionate−polyacetate metabolite. Macrolides such as **1** and its congeners may target either of the two most important cytoskeleton proteins, namely, tubulin and actin.[6] In fact, it is known that amphidinolide H (a 26-membered macrolide) stabilizes actin filaments (F-actin),[7] whereas amphidinolides X (a 16-membered ring) and J (a 15-membered ring) act as globular actin (G-actin) assembly inhibitors.[8] However, *nothing is known about the biological target of the most common amphidinolides of intermediate ring size.*

As summarized in Scheme 1, Williams and Meyer disconnected *ent*-**1** through the C6−C7 bond, which was formed by the Stille cross-coupling reaction, and through the O−C18 bond, which was formed by macrolactonization via the Mitsunobu reaction.[2] Their C7−C22 fragment was prepared via an asymmetric allylstannane addition of the C13−C22 fragment to aldehyde C7−C12 promoted by a chiral *B*-bromodiazaborolidine.[2] Lee et al. applied the Julia−Kocienski reaction for the construction of the C10−C11 double bond.[3] The enyne cross-metathesis reaction between fragments C1−C6 and C7−C10, followed by the introduction of the methyl group at C6 by using the Suzuki−Miyaura reaction, was key for the success of their strategy.[3] The Yamaguchi reaction was used for the macrolactonization.

Our approach to **1** is distinctly different, although it shares a macrolactonitzation step. It is based on the construction of the C8−C9 bond (Scheme 1) from an allylsilane (fragment **C1−C8**) and an aldehyde (fragment **C9−C22**), for which we focused our attention on stereoselective versions of the Hosomi−Sakurai reaction.[9] The starting materials for the syntheses of these two fragments would be fragments C1−C5 and C11−C22, respectively, the precursors of which were previously described by us.[4c,d]

RESULTS AND DISCUSSION

The synthesis of fragment **C1−C8** (**5**) began from a known (2*R*,4*R*)-2,4-dimethylpentanediol derivative[10] (**2**, Scheme 2), which we obtained through alkylation of the propanamide of pseudoephedrine.[11] Standard transformations gave the desired alkyne **3**. Hydrozirconation,[12] with in situ iodination, provided alkenyl iodide **4**; its enantiomer had been synthesized by another route by two of us.[2b] A Negishi coupling reaction converted **4** into the desired **5** in 88% yield.

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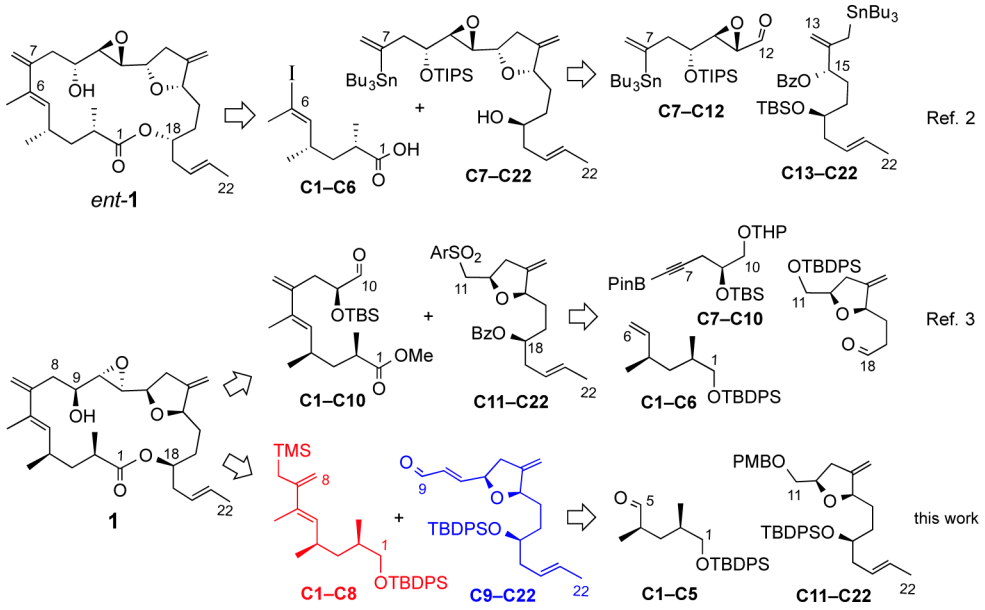
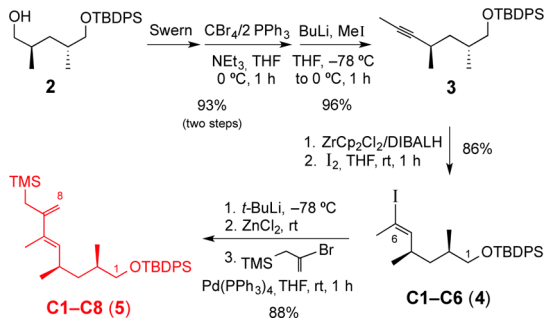
Scheme 1. Retrosynthetic Analysis of Amphidinolide K (1)

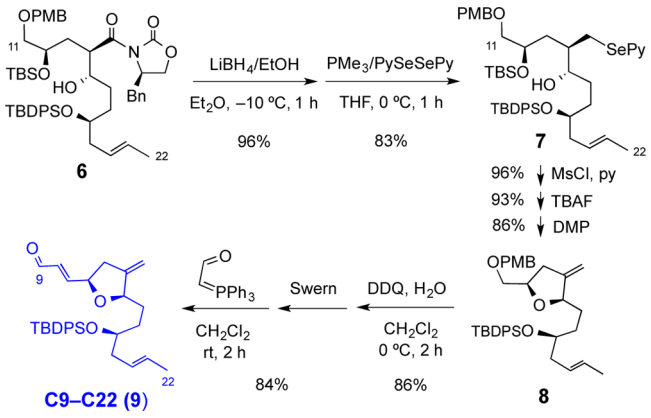


Scheme 2. Synthesis of Fragment C1−C8 (5)



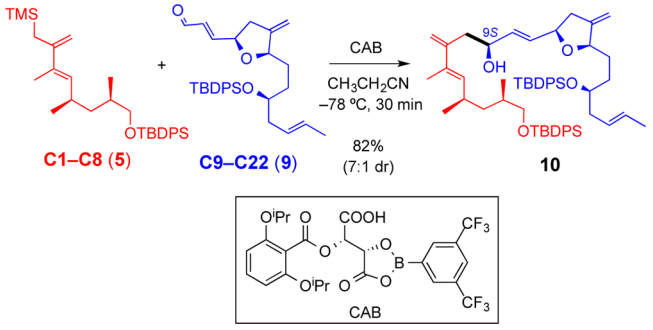
From the known[4d] C11−C22 aldol-like adduct (**6**) shown in Scheme 3, removal of the chiral auxiliary, conversion of the resulting primary alcohol to 2-pyridylselenenyl derivative **7**, cyclization to a known oxolane,[13] and elimination of the SePy at rt by oxidation with Dess−Martin periodinane (a new reaction of DMP discovered by some of us) gave **8**, a known compound.[13] A standard cleavage of the O−PMB bond and the extension of the chain (by the Swern oxidation and a Wittig reaction) allowed us to obtain the desired fragment **C9−C22** (**9**) in good overall yield.

Scheme 3. Synthesis of Fragment C9−C22 (9)



For the Hosomi−Sakurai reaction[9] between allylsilane **5** and aldehyde **9**, we first examined the catalyst developed by Yamamoto et al., a chiral (acyloxy)borane (CAB).[14] Our preliminary experiments with the catalyst prepared from the less abundant (2*S*,3*S*)-tartaric acid (Scheme 4) were satisfactory, so we optimized this procedure to the case at hand. The new stereocenter (C9-OH) was produced with good stereoselection, but 70 mol % of catalyst was required to achieve full conversion in a few hours. Eventually, bearing in mind the value of both **5** and **9**, we simply used CAB stoichiometrically to accomplish the reaction in 30 min (82% isolated yield, a 7:1 mixture by ^{1}H NMR, but only one spot on TLC with several eluents). According to the work of Yamamoto et al.,[14] we assumed that the major stereoisomer was the desired product (9*S*). It was separated from its expected stereoisomer (9*R*) at a later stage (see below).

Scheme 4. CAB-Mediated Allylation



We recognized the need to selectively deprotect the C-1 primary OH group to produce the desired carboxylic acid while maintaining protection of the chiral secondary hydroxyl substituents. Initially, we envisioned the cleavage of the two TBDPS ethers of **10** to yield the corresponding triol for conversion into its tris-*O*-TES derivative. Our application of the published procedure for the selective direct Swern oxidation of

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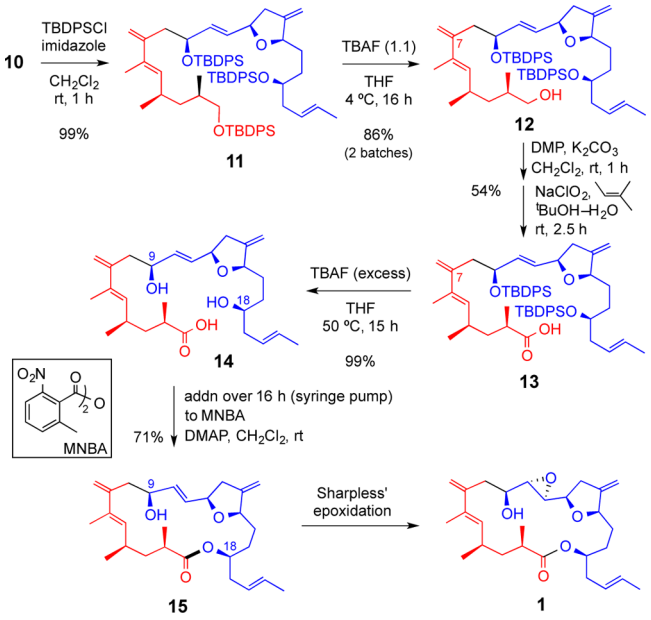
the C-1 primary TES ether was attempted.[15] However, the controlled oxidation of our tris-*O*-TES derivative gave rise to numerous byproducts.

We devised an alternative approach by protection of the C9-OH group of **10** to give the tris-TBDPS derivative (**11**), followed by the selective cleavage[16] of the C1 primary silyl ether to obtain the desired **12** (Scheme 5). First, we examined a

Scheme 5. Final Steps



model substrate containing TBDPS-protected primary and secondary hydroxy groups, $CH_3CH(OTBDPS)$-$CH_2CH_2CH_2CH_2OTBDPS$, and we optimized conditions for the deprotection of the primary silyl ether. After investigating the performance of TBAF, TBAF/RCOOH, $Et_3N{\cdot}3HF$, and $(HF)_x{\cdot}$py in varying amounts at different times and temperatures, we found that the best procedure was to use stoichiometric amounts of TBAF with stirring at 4 °C overnight. In fact, the reactions with the other sources of fluoride ion and with TBAF/PhCOOH at −20 °C were too slow to be effective, whereas forcing the conditions gave mixtures of deprotected diols. In practice, we treated **11** with TBAF at 4 °C overnight, providing a yield of 64% of **12** with recovery of 35% of **11** after separation by column chromatography. The recovered starting material, **11**, was resubjected to the same deprotection treatment to afford 22% of **12** (86% overall yield), and the remaining starting material, **11**, was once again recovered. Oxidation of **12** to the corresponding aldehyde with DMP proved to be superior to the Swern oxidation, which caused partial isomerization (migration of the C7 exocyclic double bond to position C7−C8). Without purification, the intermediate aldehyde was subjected to standard oxidation to the carboxylic acid **13**, and complete deprotection yielded the desired dihydroxy acid, **14**.

We attempted the direct cyclization of this dihydroxyacid. In principle, under the usual high-dilution conditions (HDC) required for macrocyclization reactions, the formation of the 10-membered macrolide should be disadvantageous in relation to the formation of the 19-membered ring.[17] We would thus circumvent the requirement for selective protection of the secondary hydroxy group at C9 in the presence of the secondary hydroxy group at C18.

In trial macrolactonization experiments, the Yamaguchi method (i.e., addition of $ArCOCl/Et_3N$, where Ar = 2,4,6-trichlorophenyl, in THF or toluene, filtration of $Et_3NH^+Cl^-$, and slow addition of the solution via a syringe pump into a large excess of DMAP in a suitable refluxing solvent)[18] gave the desired 19-membered lactone **15**, which was contaminated with the C9 2,4,6-trichlorobenzoate derivative (C9-OCOAr). This result suggested that the free hydroxy group at C9 did not compete in the intramolecular cyclization but was involved in an acylation reaction with the $DMAP^+-COAr$ intermediate.

Alternatively, cyclization of **14** with 2-methyl-6-nitrobenzoic anhydride (MNBA, 1.1 equiv) and DMAP in CH_2Cl_2,[19] also under HDC, provided **15** in 71% yield and assumed to be C9 epimer (*epi*-**15**) in 10% yield (macrocyclization yield of 81%!). Under these conditions, the C9-OCOAr contaminant, with Ar = 2-methyl-6-nitrophenyl, and cyclic dimers as well as open-chain dimers were not observed. Compounds **15** and *epi*-**15** could be readily separated by flash chromatography. Thus, whereas **10**−**14** were contaminated (likely with the corresponding epimers at C9), the desired macrolactone **15** was isolated in a pure state. Its NMR spectra and specific rotation were identical to those of the compound reported by Lee et al.[3] (see the Experimental Section). Via a Hosomi−Sakurai reaction between **5** and **9** using the enantiomer of CAB derived from the most abundant (2*R*,3*R*)-tartaric acid (L-tartaric acid), we obtained a sample of *epi*-**10** (now with **10** as the minor product); NMR spectra of **10** and *epi*-**10** are compared in the Supporting Information.

The Sharpless asymmetric epoxidation [^{t}BuOOH, $Ti(O^iPr)_4$, (+)-DET] of **15** gave **1**, as had been reported by Lee et al.,[3] with complete conversion. The NMR spectral data agreed with those reported[1,3] (see Table 1). Thus, an independent, convergent total synthesis of **1** has been accomplished, with most steps in yields ≥80%.

(−)-Amphidinolide K (**1**) is known to be cytotoxic (IC_{50} = 4.0 μM for murine lymphoma cells and IC_{50} = 6.5 μM for human epidermoid carcinoma cells).[5a] As already mentioned, we were interested in elucidating the biological target and binding site of **1** (and of their isomers and analogs). In the family of compounds to be examined, we included **15** as well as *epi*-**15** (which we also prepared from *epi*-**10**, by means of the sequence of reactions shown in Scheme 5). In order to increase the number of isomeric epoxides to be screened, we attempted to epoxidize **15** with (−)-DET under the same conditions as reported for the Sharpless epoxidation of **15** with (+)-DET, unsuccessfully (as the starting material was recovered unchanged). Moreover, when we attempted to epoxidize *epi*-**15**, either with (+)-DET or (−)-DET, complex mixtures of products were obtained. We also examined the biological target of (+)-amphidinolide K (*ent*-**1**) and diastereoisomers of *ent*-**1** (so-called WM1 and WM2 in Figure 1) obtained years ago.[2]

None of the six compounds in Figure 1 were active as microtubule stabilizers or destabilizers; in other words, these macrocycles do not affect the α,β-tubulin−microtubule equilibrium. The effect of these compounds on actin polymerization was also examined, using purified actin from rabbit skeletal muscle,[21] with phalloidin (stabilizer of F-actin) and cytochalasin B (stabilizer of monomeric G-actin) as reference compounds. In these in vitro experiments, **1** showed a strong stabilizing effect on F-actin (approximately 70% that of phalloidin), while *ent*-**1** produced a moderate stabilizing effect

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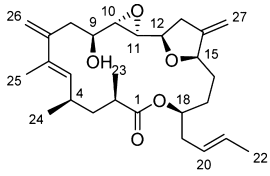
Table 1. Comparison of ^{1}H and ^{13}C NMR Chemical Shifts of (−)-Amphidinolide K (1) in C_6D_6



1

	Kobayashi et al. (ref 1)		Lee et al. (ref 3)		this work	
position	δ^1H	δ^{13}C	δ^1H	δ^{13}C	δ^1H[a]	δ^{13}C[b]
1		175.4		175.4		175.4
2	2.48	38.0	2.51−2.44	38.1	2.44	38.1
3 (a)	1.96	41.4	1.96	41.4	1.93	41.5
3 (b)	1.08		1.08		1.06−0.99	
4	2.98	30.9	3.02−2.93	31.0	2.94	31.0
5	5.36	134.4	5.35	134.5	5.32	134.5
6		134.2		133.7		133.8
7		145.7		145.6		145.7
8 (a)	3.27	39.9	3.28	40.0	3.24	40.0
8 (b)	2.34		2.34		2.30	
9	4.37	65.6	4.38	65.6	4.34	65.7
10	3.22	56.8	3.21	56.9	3.18	56.9
11	2.86	56.0	2.86	56.0	2.82	56.0
12	4.05	74.2	4.06−4.03	74.2	4.01	74.3
13 (2H)	2.55	36.0	2.55−2.53	36.0	2.53−2.49	36.1
14		151.5		151.5		151.5
15	4.19	80.8	4.18	80.8	4.15	80.8
16 (a)	1.86	29.1	1.92−1.85	29.1	1.85−1.82	29.2
16 (b)	1.60		1.63−1.57		1.60−1.54	
17 (a)	1.89	30.0	1.92−1.85	30.0	1.85−1.82	30.0
17 (b)	1.58		1.63−1.57		1.60−1.54	
18	5.27	71.6	5.29−5.24	71.6	5.23	71.7
19 (a)	2.39	35.9	2.41−2.36	35.9	2.36	35.9
19 (b)	2.16		2.17−2.11		2.11	
20	5.39	126.9	5.45−5.38	126.9	5.43−5.34	127.0[c]
21	5.41	128.8		126.9		127.0[c]
22 (3H)	1.56	18.0	1.55	18.0	1.52	18.1
23 (3H)	1.14	19.2	1.14	19.3	1.10	19.3
24 (3H)	0.92	21.3	0.92	21.4	0.88	21.4
25 (3H)	1.84	14.5	1.84	14.6	1.80	14.6
26 (a)	5.12	114.0	5.12	114.0	5.08	114.1
26 (b)	4.96		4.96		4.92	
27 (a)	4.92	104.1	4.92	104.1	4.89	104.2
27 (b)	4.75		4.74		4.71	

[a]Referred to the signal of C_6D_5H in C_6D_6 (δ 7.16).[20] [b]Referred to the solvent signal (δ 128.06).[20] [c]HSQC experiments suggested that these two carbon atoms are fortuitously isochronous.

(30% that of phalloidin). Neither **15** nor *epi*-**15**, both lacking the epoxide groups, interacted with F-actin; WM1 and WM2 did not stabilize F-actin either. These results provide preliminary data as a baseline for additional experiments. In the future, we plan to examine and compare additional samples of amphidinolides, other than those in Figure 1, to gain more insight into the interaction of different subfamilies of amphidinolides with actin-binding sites.

CONCLUSION

A second route for the total synthesis of natural amphidinolide K (**1**) has been accomplished after years of effort. A crucial step has applied the Hosomi−Sakurai reaction to advanced

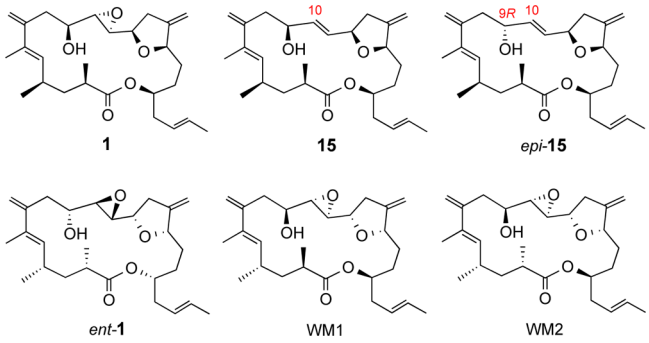


Figure 1. Compounds investigated as potential tubulin- or actin-binding agents.

fragments such as **5** and **9**. The macrolactonization reaction, the penultimate step in many syntheses of macrolides, which is often problematic, was achieved using the Shiina mixed anhydride reagent. A summary of the key reactions and catalysts involved is indicated in Figure 2. The natural product (**1**) showed significant stabilizing activity of F-actin in vitro.

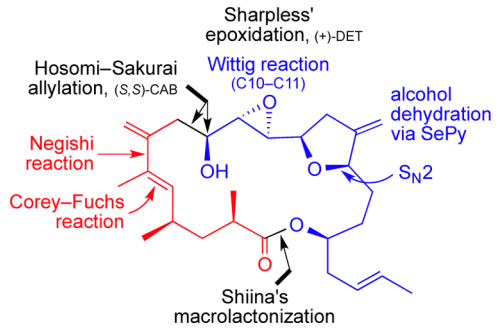


Figure 2. Summary of the main transformations and the sources of chirality.

EXPERIMENTAL SECTION

General Methods. Unless specified otherwise, all starting materials and reagents were obtained from commercial suppliers and used without further purification. All reactions were conducted in oven-dried glassware, under dry nitrogen, with anhydrous solvents, which were dried and distilled before use according to standard procedures. Solvents used for isolation of products and chromatography were glass distilled. Analytical thin-layer chromatography (TLC) was performed on 0.25 mm silica gel plates (F_{254}); retention factors (R_f) are approximate. Flash column chromatography was performed on silica gel (35−70 μm). Yields were determined after purification of the desired compound by flash column chromatography on silica gel and removal of last traces of solvent (high vacuum, up to constant weight). ^{1}H NMR spectra were recorded on 400 MHz spectrometers, unless otherwise indicated (500 MHz); chemical shifts are reported in ppm, in $CDCl_3$ unless otherwise indicated (C_6D_6), with TMS as internal reference or with the solvent resonance as the internal standard ($CHCl_3$ impurity in $CDCl_3$, δ 7.26 ppm; benzene-d_5 in C_6D_6, δ 7.16 ppm); data are reported in the following order: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, br = broad, m = multiplet), coupling constants (Hz), integration. ^{13}C NMR spectra were recorded in $CDCl_3$, unless otherwise indicated (C_6D_6), on the above-mentioned spectrometers (100.6 Mz for ^{13}C), unless otherwise indicated (125.7 MHz), with complete proton decoupling (BB) and DEPT; chemical shifts are reported in ppm with the solvent as the internal standard ($CDCl_3$, δ 77.2 ppm, C_6D_6 δ 128.1 ppm). Where necessary, 2D NMR experiments (HSQC and NOESY) were carried out to assist in

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structure elucidation and signal assignments. Optical rotations were measured on a polarimeter at 20 °C (cuvette of 1 mL) and are reported as follows: $[\alpha]_D$ (c in g/100 mL, solvent). The high-resolution mass spectra (HRMS) were obtained by the electrospray ionization (ESI, TOF) technique in positive or negative mode (as indicated).

(4*R*,6*R*)-7-[(*tert*-Butyldiphenylsilyl)oxy]-4,6-dimethyl-2-heptyne (3). Freshly distilled oxalyl chloride (0.228 mL, 2.70 mmol) was added dropwise to a solution of anhydrous dimethyl sulfoxide (0.390 mL, 5.26 mmol) in dichloromethane (6.5 mL) at at −78 °C. After 30 min, a solution of the starting material, the known alcohol[4c,10,11] (2*R*,4*R*)-5-[(*tert*-butyldiphenylsilyl)oxy]-2,4-dimethyl-1-pentanol, **2** (0.500 g, 1.35 mmol), in anhydrous dichloromethane (6.5 mL) was added to the reaction mixture at −78 °C. Thirty minutes later, anhydrous triethylamine (ca. 0.90 mL, 0.655 g, 6.48 mmol) was added at −78 °C, and the reaction was allowed to warm to room temperature and stirred for 30 min. The reaction was quenched with NH_4Cl solution (5 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated under reduced pressure to afford an oily residue (pure on TLC and NMR analysis, the corresponding aldehyde, full conversion). This oil and triethylamine (0.56 mL, 4.07 mmol) were dissolved in dichloromethane (4 mL) and cooled to 0 °C. In a separate flask, CBr_4 (1.034 g, 3.12 mmol) and PPh_3 (1.67 g, 6.37 mmol) were carefully mixed in dichloromethane (7 mL) and stirred at 0 °C until the solution acquired a strong orange color. It was then cannulated into the previously prepared solution of the aldehyde at 0 °C and stirred for 45 min at this temperature. The reaction was quenched with NH_4Cl solution (5 mL) and extracted with diethyl ether (3 × 10 mL). The organic extracts were dried over $MgSO_4$ and filtered, and the solvent was evaporated. The residue was purified by flash chromatography (5% ethyl acetate in hexanes) to provide the desired dibromoalkene (0.663 g, 93% over two steps).

Butyllithium (1.6 M in hexanes, 2.1 mL, 3.4 mmol) was slowly added to a solution of the dibromide (0.663 g, 1.26 mmol) in dry THF (13 mL) at −78 °C. After 1 h, iodomethane (1.790 g, 12.6 mmol) was added at −78 °C, and the reaction was allowed to warm to room temperature for another 1 h. The reaction was quenched with NH_4Cl (5 mL) and extracted three times with diethyl ether, and the organic extracts were dried, filtered, and evaporated. The crude product was purified by flash chromatography (5% ethyl acetate in hexanes) to obtain **3** (0.460 g, 96%) as a colorless oil: R_f (5% EtOAc in hexanes) 0.70; ^{1}H NMR δ 7.66 (m, 4H), 7.44−7.34 (m, 6H), 3.55 (dd, J = 9.8, 5.0, 1H), 3.47 (dd, J = 9.9, 5.9, 1H), 2.44−2.32 (m, 1H), 1.88 (m, 1H), 1.76 (d, J = 2.3, 3H), 1.53−1.43 (m, 1H), 1.26 (ddd, J = 13.3, 8.8, 6.3 Hz, 1H), 1.08 (d, J = 6.8 Hz, 3H), 1.05 (s, 9H), 0.97 (d, J = 6.8 Hz, 3H); ^{13}C NMR δ 135.8, 135.8, 134.2, 134.2, 129.6, 129.6, 127.7, 84.3, 75.5, 68.3, 41.2, 33.8, 27.0, 23.8, 21.7, 19.5, 17.8, 3.7; $[\alpha]_D$ = −12.1 (CH_2Cl_2, c 1.24); HRMS (ESI+) m/z calcd for $C_{25}H_{35}OSi^+$ (M + H)$^+$ 379.2452, found 379.2461.

(2*E*,4*R*,6*R*)-7-[(*tert*-Butyldiphenylsilyl)oxy]-2-iodo-4,6-dimethyl-2-heptene (4). DIBALH (1.63 mL of 1 M THF solution, 1.63 mmol) was added to a solution of $ZrCp_2Cl_2$ (0.47 g, 1.57 mmol) in dry THF (5 mL) at 0 °C. After 30 min, the alkyne **2** (0.460 g, 1.21 mmol) in THF (2 mL) was added via cannula to the mixture at 0 °C. When the alkyne disappeared (around 1 h), a solution of iodine (0.461 g, 1.82 mmol) in dry THF (2 mL) was added at 0 °C, and the reaction was allowed to warm to room temperature for 1 h. The final solution was concentrated in vacuo and the crude product was purified by flash chromatography (1% EtOAc in hexanes) to afford iodoalkene **4** (86%, 0.526 g) as a colorless oil: R_f (EtOAc in hexanes) 0.60; ^{1}H NMR δ 7.68−7.62 (m, 4H), 7.44−7.33 (m, 6H), 5.92 (dq, J = 9.8, 1.4, 1H), 3.50 (dd, J = 9.8, 5.1, 1H), 3.40 (dd, J = 9.8, 6.0, 1H), 2.45−2.28 (m, 1H), 2.22 (d, J = 1.5, 3H), 1.71−1.58 (m, 1H), 1.47−1.36 (m, 1H), 1.05 (s, 9H), 1.03−0.97 (m, 1H), 0.94 (d, J = 6.7, 3H), 0.89 (d, J = 6.7, 3H); ^{13}C NMR δ 147.8, 135.8, 135.8, 134.1, 129.7, 127.8, 127.8, 92.4, 68.4, 40.5, 33.5, 33.5, 29.9, 27.7, 27.1, 20.5, 19.5, 17.7; $[\alpha]_D$ = −25.5 (CH_2Cl_2, c 1.03); HRMS (ESI+) m/z calcd for $C_{25}H_{36}IOSi^+$ (M + H)$^+$ 507.1575, found 507.1567.

(3*E*,5*R*,7*R*)-8-[(*tert*-Butyldiphenylsilyl)oxy]-3,5,7-trimethyl-2-(trimethylsilylmethyl)-1,3-octadiene (5). A 1.7 M solution of ^{t}BuLi in pentane (1.11 mL, 1.89 mmol) was added dropwise to a stirring solution of (2-bromoallyl)trimethylsilane (0.164 mL, 0.86 mmol) in anhydrous THF (3 mL) at −78 °C. After 20 min, the resulting solution was added dropwise via cannula to a solution of anhydrous $ZnCl_2$ (0.117 g, 0.86 mmol) in THF (5 mL), and the mixture was left to warm to room temperature for 30 min. The organozinc solution was then slowly added via cannula to a solution of iodide **3** (0.291 g, 0.572 mmol) and $Pd(PPh_3)_4$ (66 mg, 0.057 mmol) in THF (3 mL) prepared in a flame-dried flask under Ar. After being stirred for 20 min at room temperature, the mixture was quenched with pH 7 buffer (5 mL). The phases were separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic fractions were washed with water (5 mL), dried over $MgSO_4$, and concentrated. The crude product was purified by flash chromatography (hexanes/ethyl acetate, 99:1) to afford allylsilane **5** (248 mg, 88%) as a colorless oil: R_f (1% ethyl acetate in hexanes) 0.60; ^{1}H NMR δ 7.67 (m, 4H), 7.46−7.33 (m, 6H), 5.29 (d, J = 8.8, 1H), 4.86 (d, J = 1.7, 1H), 4.65 (s, 1H), 3.51 (dd, J = 9.8, 5.1, 1H), 3.43 (dd, J = 9.7, 6.1, 1H), 2.55−2.43 (m, 1H), 1.77 (d, J = 2.8, 2H), 1.70 (d, J = 0.8, 3H), 1.69−1.65 (m, 1H), 1.49−1.41 (m, 1H), 1.12−1.06 (m, 1H), 1.06 (s, 9H), 0.95 (d, J = 6.7, 3H), 0.91 (d, J = 6.6, 3H), −0.02 (s, 9H); ^{13}C NMR δ 147.5, 135.8, 135.2, 134.2, 133.2, 129.6, 127.7, 108.3, 68.7, 41.2, 33.6, 30.6, 27.0, 24.1, 20.9, 19.5, 17.6, 14.4, −0.9; $[\alpha]_D$ = −12.2 (CH_2Cl_2, c 0.85); HRMS (ESI+) m/z calcd for $C_{31}H_{49}OSi_2^+$ (M + H)$^+$ 493.3316, found 493.3329.

(2*R*,4*R*,5*S*,8*S*,10*E*)-2-[(*tert*-Butyldimethylsilyl)oxy]-8-[(*tert*-butyldiphenylsilyl)oxy]-1-[(4-methoxybenzyl)oxy]-4-(2-pyridylselenenylmethyl)-10-dodecen-5-ol (7). $LiBH_4$ (2 M solution in THF, 0.14 mL, 0.28 mmol) was added to a cooled (−20 °C) solution of a known aldol[4d] (**6**, Scheme 3, 206 mg, 0.23 mmol) and ethanol (16 μL, 0.27 mmol) in anhydrous diethyl ether (4 mL) under N_2. The reaction mixture was stirred for 1 h at −10 °C before being quenched with a saturated $NaHCO_3$ solution (4 mL) and extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with water (4 mL) and brine (4 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The product was purified by flash chromatography (hexanes/ethyl acetate, 70:30) to yield 161 mg (96%) of the desired diol intermediate, (2*S*,3*S*,6*S*,8*E*)-2-[(2*R*)-2-[(*tert*-butyldimethylsilyl)oxy]-3-[(4-methoxybenzyl)oxy]propyl]-6-[(*tert*-butyldiphenylsilyl)oxy]-8-decene-1,3-diol, as a colorless oil: R_f (30% ethyl acetate in hexanes) 0.37; ^{1}H NMR δ 7.67 (m, 4H), 7.43−7.34 (m, 6H), 7.24 (m, 2H), 6.87 (m, 2H), 5.28 (m, 2H), 4.43 (m, 2H), 3.94 (m, 1H), 3.80 (s, 3H), 3.80−3.71 (m, 2H), 3.64−3.60 (m, 2H), 3.40 (dd, J = 9.5, 5.7, 1H), 3.33 (dd, J = 9.5, 5.9, 1H), 2.19−2.08 (m, 2H), 1.73 (m, 1H), 1.63−1.35 (m, 6H), 1.57 (d, 4.2 Hz, 3H), 1.05 (s, 9H), 0.87 (s, 9H), 0.05 (s, 6H); ^{13}C NMR δ 159.3, 136.1, 136.0, 134.6, 130.3, 129.7, 129.6, 129.4, 129.1, 127.6, 127.6, 127.4, 113.9, 76.0, 74.5, 73.3, 73.1, 69.7, 65.1, 55.4, 40.5, 39.9, 32.5, 30.3, 29.2, 27.2, 26.0, 19.5, 18.3, 18.1, −4.1, −4.7; $[\alpha]_D$ = +4.6 (CH_2Cl_2, c 0.85); HRMS (ESI+) m/z calcd for $C_{43}H_{66}NaO_6Si_2^+$ (M + Na)$^+$ 757.4290, found 757.4288. Trimethylphosphine (1 M in THF or toluene, 0.83 mL, 0.83 mmol) and 2,2′-dipyridyl diselenide, PySeSePy, 0.065 g, 0.22 mmol) were added to a solution of the diol just described (0.120 g, 0.16 mmol) in 12 mL of anhydrous THF at 0 °C. After 1 h, the reaction was diluted with water (5 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The product was purified by flash chromatography (hexanes/ethyl acetate, 80:20) to provide 7 (0.119 g, 83%) as a yellow oil: R_f (30% EtOAc in hexanes) 0.48; ^{1}H NMR δ 8.35 (ddd, J = 5.0, 1.8, 0.9, 1H), 7.67−7.62 (m, 4H), 7.44 (ddd, J = 8.0, 7.3, 1.9, 1H), 7.40−7.29 (m, 7H), 7.24 (m, 2H), 7.03 (ddd, 7.2, 5.0, 1.2, 1H), 6.86 (m, 2H), 5.25 (m, 2H), 4.42 (s, 2H), 3.95 (m, 1H), 3.80 (s, 3H), 3.78 (m, 1H), 3.73 (quint, J = 5.9, 1H), 3.38 (dd, J = 9.5, 5.8, 1H), 3.35−3.28 (m, 2H), 3.21 (dd, J = 13.3, 4.2, 1H), 2.09−2.01 (m, 2H), 1.82 (m, 1H), 1.66−1.33 (m, 6H), 1.53 (dd, J = 3.4, 1.1, 3H), 1.02 (s, 9H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR δ 159.2, 156.6, 150.0, 136.2, 136.1, 136.1, 134.9, 134.7, 130.6, 129.5, 129.5, 129.4, 127.6, 127.5, 127.3, 125.9, 120.5, 113.9, 75.6, 73.5, 73.1, 71.3, 69.6, 55.4, 53.6, 40.5, 39.8, 33.4, 33.0, 29.0, 28.0, 27.2, 26.1, 19.5, 18.3, 18.2, −3.8, −4.6; $[\alpha]_D$ = −6.2

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(CH_2Cl_2, *c* 1.02); HRMS (FAB) *m*/*z* calcd for $C_{48}H_{70}NO_5SeSi_2$ ($M + H^+$) 876.3952, found 876.3964.

Formation of the Oxolane (Tetrahydrofuran) Ring. Methanesulfonyl chloride (MsCl, 0.246 mL, 3.18 mmol) was added to a solution of alcohol **7** (0.700 g, 0.796 mmol) in anhydrous pyridine (5 mL) at 0 °C under N_2. The mixture was stirred for 5 h at rt, and then pyridine was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (20% ethyl acetate in hexanes) to afford the mesylate intermediate, (2*E*,5*S*,8*S*,9*R*,11*R*)-11-[(*tert*-butyldimethylsilyl)oxy]-5-[(*tert*-butyldiphenylsilyl)oxy]-12-[(4-methoxybenzyl)oxy]-8-[(methylsulfonyl)oxy]-9-(2-pyridylselenenylmethyl)-2-dodecene[13] (731 mg, 96%): R_f (30% EtOAc in hexanes) 0.5; ^{1}H NMR δ 8.40 (ddd, *J* = 4.9, 1.8, 0.8, 1H), 7.67 (m, 4H), 7.44−7.29 (m, 8H), 7.23 (m, 2H), 7.01 (ddd, *J* = 7.3, 4.9, 1.0, 1H), 6.87 (m, 2H), 5.28 (m, 2H), 4.81 (m, 1H), 4.42 (m, 2H), 4.01 (quint, *J* = 5.6, 1H), 3.80 (s, 3H), 3.73 (quint, *J* = 5.3, 1H), 3.43−3.35 (m, 2H), 2.90 (s, 3H), 2.29 (m, 1H), 2.10 (m, 2H), 1.83 (m, 1H), 1.63−1.49 (m, 5H), 1.57 (d, *J* = 4.9, 3H), 1.04 (s, 9H), 0.83 (s, 9H), 0.05 (s, 3H), 0.00 (s, 3H); ^{13}C NMR δ 159.2, 155.1, 150.0, 136.0, 136.0, 136.0, 134.5, 134.4, 130.5, 129.7, 129.6, 129.4, 127.8, 127.7, 127.6, 127.0, 125.6, 120.4, 113.8, 86.5, 75.0, 73.0, 72.9, 69.2, 55.4, 39.9, 38.8, 38.5, 35.2, 31.9, 27.3, 27.2, 27.1, 26.5, 26.1, 19.5, 18.2, 18.2, −4.0, −4.6. A solution of this mesylate (222 mg, 0.23 mmol) in anhydrous THF (4.1 mL) was cooled to 0 °C, and TBAF·$3H_2O$ (110 mg, 0.35 mmol) was added under N_2. The mixture was stirred at 4 °C during 40 h and was then directly purified by flash chromatography (20% EtOAc in hexanes) to give the oxolane C11−C22 intermediate[13] (159 mg, 93%) as a pale yellow oil: R_f (20% EtOAc in hexanes) 0.4; ^{1}H NMR δ 8.37 (m, 1H), 7.69 (m, 4H), 7.38 (m, 7H), 7.26 (m, 3H), 6.99 (ddd, *J* = 7.2, 4.9, 1.0, 1H), 6.86 (m, 2H), 5.30 (m, 2H), 4.50 (d, *J* = 11.8, 1H), 4.44 (d, *J* = 11.8, 1H), 4.01 (m, 1H), 3.80 (s, 3H), 3.79−3.71 (m, 2H), 3.44 (m, 2H), 3.25 (dd, *J* = 11.9, 4.9, 1H), 2.92 (t, *J* = 11.3, 1H), 2.48 (m, 1H), 2.23−2.10 (m, 3H), 1.75−1.43 (m, 5H), 1.56 (m, 3H), 1.06 (s, 9H); ^{13}C NMR δ 159.2, 155.4, 150.1, 136.1, 136.1, 135.9, 134.8, 134.6, 130.6, 129.6, 129.6, 129.4, 127.6, 127.5, 127.5, 127.4, 125.5, 120.3, 113.8, 82.5, 77.3, 73.5, 73.1, 73.1, 55.4, 41.7, 40.3, 35.0, 33.1, 27.2, 26.8, 26.6, 19.6, 18.2; $[\alpha]_D$ = −9.8 (CH_2Cl_2, *c* 1.07); HRMS (ESI+) *m*/*z* calcd for $C_{42}H_{54}NO_4SeSi$ $(M + H)^+$ 744.2982, found 744.2980.

Deselenenylation Reaction.[13] DMP (0.54 g, 1.23 mmol) was added to a solution of the oxolane C11−C22 fragment (305 mg, 0.41 mmol) in anhydrous CH_2Cl_2 (2 mL) at 0 °C. After being stirred for 1 h at rt, the mixture was vigorously stirred with aq Na_2CO_3, and the reaction was checked by TLC analysis (20% EtOAc in hexanes). The organic compound was extracted with dichloromethane, dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography (20% EtOAc in hexanes) to give the deselenenylated C11−C22 fragment, (2*R*,5*R*)-tetrahydro-2-[(3*S*,5*E*)-3-[(*tert*-butyldiphenylsilyl)-oxy]-5-hepten-1-yl]-5-[(4-methoxyphenylmethoxy)methyl]-3-methylenefuran (**8**) (211 mg, 86%) as a colorless oil: R_f (20% EtOAc in hexanes) 0.45; ^{1}H NMR δ 7.68−7.66 (m, 4H), 7.41−7.32 (m, 6H), 7.25 (d, *J* = 8.6, 2H), 6.86 (d, *J* = 8.6, 2H), 5.28 (m, 2H), 4.89 (q, *J* = 1.9, 1H), 4.68 (q, *J* = 2.0, 1H), 4.52 (d, *J* = 11.8, 1H), 4.45 (d, *J* = 11.8, 1H), 4.20 (m, 1H), 4.03 (m, 1H), 3.79 (s, 3H), 3.72 (m, 1H), 3.43 (m, 2H), 2.54 (dd, *J* = 15.6, 6.0, 1H), 2.24 (m, 1H), 2.10 (m, 2H), 1.67 (m, 2H), 1.56 (d, *J* = 3.9, 3H), 1.53−1.41 (m, 3H), 1.05 (s, 9H); ^{13}C NMR δ 159.3, 151.1, 136.1, 136.1, 134.7, 130.5, 129.5, 129.5, 127.5, 127.5, 127.5, 127.4, 113.9, 104.6, 81.4, 77.4, 73.5, 73.2, 72.4, 55.4, 40.0, 36.5, 31.9, 30.8, 27.2, 19.6, 18.2; $[\alpha]_D$ = −6.5 (CH_2Cl_2, *c* 1.03); HRMS (ESI+) *m*/*z* calcd for $C_{37}H_{49}O_4Si$ $(M + H)^+$ 585.3395, found 585.3408.

Compound 9, (2*E*)-3-[(2*S*,5*R*)-Tetrahydro-5-[(5*E*)-3-[(*tert*-butyldiphenylsilyl)oxy]-5-heptenyl]-4-methylene-2-furanyl]-2-propenal. DDQ (2,3-dichloro-5,6-dicyanobenzoquinone, 108 mg, 0.476 mmol) was added to a solution of **8** (557 mg, 0.952 mmol) in CH_2Cl_2/H_2O (10:1, 10 mL) at 0 °C, and after 30 min, more DDQ (108 mg, 0.476 mmol) was added. The reaction was stirred for 2 h at 0 °C. The phases were separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried with $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The crude was purified by flash chromatography (20% EtOAc in hexanes) to give the PMB-deprotected alcohol intermediate[13] (385 mg, 86%) as a colorless oil: R_f (20% EtOAc in hexanes) 0.28; ^{1}H NMR δ 7.67 (m, 4H), 7.44−7.33 (m, 6H), 5.31 (m, 2H), 4.92 (br s, 1H), 4.70 (br s, 1H), 4.21 (m, 1H), 3.97 (m, 1H), 3.74 (m, 2H), 3.47 (m, 1H), 2.49 (dd, *J* = 15.6, 6.2, 1H), 2.38 (m, 1H), 2.12 (m, 2H), 1.80−1.45 (m, 4H), 1.58 (d, *J* = 4.5, 3H), 1.05 (s, 9H); ^{13}C NMR δ 151.1, 136.1, 136.1, 134.7, 129.6, 129.6, 127.6, 127.5, 127.5, 127.4, 104.9, 81.4, 78.2, 73.3, 64.5, 40.0, 34.6, 31.9, 30.8, 27.2, 19.5, 18.2; $[\alpha]_D$ = −9.5 (CH_2Cl_2, *c* 1.03); HRMS (ESI+) *m*/*z* calcd for $C_{29}H_{41}O_3Si$ $(M + H)^+$ 465.2819, found 465.2831. Oxalyl chloride (ClCOCOCl, 0.098 mL, 1.162 mmol) was added dropwise to a solution of anhydrous dimethyl sulfoxide (0.168 mL, 2.27 mmol) in anhydrous dichloromethane (3 mL) at −78 °C for 30 min. The alcohol (0.270 g, 0.58 mmol) in CH_2Cl_2 (3 mL) was then added dropwise via cannula, and the reaction mixture was stirred for 30 min at −78 °C. Anhydrous Et_3N (0.4 mL, 2.79 mmol) was added at −78 °C, and the reaction was stirred at rt for 30 min. After quenching with NH_4Cl, the phases were separated, and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The resulting yellow oil was dissolved in anhydrous dichloromethane (5 mL), and (triphenylphosphoranylidene)-acetaldehyde (0.266 g, 0.875 mmol) was added. The reaction was stirred for 2 h at rt. The mixture was directly concentrated and purified by flash chromatography (20% ethyl acetate in hexanes) to afford the desired enal, **9**, as a colorless oil (239 mg, 84%): R_f (20% EtOAc in hexanes) 0.30; ^{1}H NMR δ 9.55 (d, *J* = 7.9, 1H), 7.68 (m, 4H), 7.44−7.33 (m, 6H), 6.76 (dd, *J* = 15.7, 5.1, 1H), 6.27 (ddd, *J* = 15.7, 7.9, 1.3, 1H), 5.32 (m, 2H), 4.96 (dt, *J* = 2.5, 1.7, 1H), 4.75 (dt, *J* = 2.9, 1.9, 1H), 4.53 (dddd, *J* = 9.9, 6.4, 5.1, 1.4, 1H), 4.27 (m, 1H), 3.76 (m, 1H), 2.77 (ddd, *J* = 15.6, 6.3, 0.7, 1H), 2.32 (dddd, *J* = 15.1, 9.9, 4.8, 2.6, 1H), 2.14 (m, 2H), 1.70 (m, 2H), 1.59 (d, *J* = 4.5, 3H), 1.49 (m, 2H), 1.06 (s, 9H); ^{13}C NMR δ 193.6, 155.6, 149.8, 136.1, 136.1, 134.7, 134.6, 131.4, 129.6, 127.7, 127.6, 127.6, 127.3, 105.5, 81.7, 76.6, 73.3, 40.0, 39.3, 31.8, 30.8, 27.2, 19.6, 18.2; $[\alpha]_D$ = −8.5 (CH_2Cl_2, *c* 0.93); HRMS (FAB) *m*/z calcd for $C_{31}H_{41}O_3Si$ $(M + H)^+$ 489.2819, found 489.2824.

CAB-Mediated Allylation. Synthesis of (1*E*,3*S*,6*E*,8*R*,10*R*)-11-[(*tert*-Butyldiphenylsilyl)oxy]-1-[(2*S*,5*R*)-tetrahydro-5-[(3*S*,5*E*)-3-[(*tert*-butyldiphenylsilyl)oxy]-5-heptenyl]-4-methylene-2-furanyl]-6,8,10-trimethyl-5-methylene-1,6-undecadien-3-ol (10). A solution of 3,5-bis(trifluoromethyl)phenylboronic acid (0.098 g, 0.266 mmol) and D-tartrate ligand[14a] (0.069 g, 0.266 mmol) in dry propanenitrile (1 mL) was stirred at rt for 15 h. Allylsilane **5** (0.159 g, 0.323 mmol) and aldehyde **9** (0.130 g, 0.266 mmol) in dry propanenitrile (2.5 mL) were then added simultaneously via cannula at −78 °C. After 30 min at −78 °C, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with Et_2O. The combined organic extracts were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (10% to 20% ethyl acetate in hexanes) to afford **10** (98 mg, 82%, dr 7:1) as a colorless oil: R_f (20% EtOAc in hexanes) 0.30; ^{1}H NMR δ 7.71−7.63 (m, 8H), 7.43−7.32 (m, 12H), 5.77 (dd, *J* = 15.5, 5.4, 1H), 5.70 (dd, *J* = 15.5, 6.7, 1H), 5.35 (d, *J* = 9.5, 1H), 5.28 (m, 2H), 5.10 (d, *J* = 1.6, 1H), 4.93 (br s, 1H), 4.89 (d, *J* = 1.6, 1H), 4.75 (br s, 1H, minor) 4.67 (br s, 1H, major), 4.22 (m, 1H), 3.76−3.71 (m, 1H), 3.50 (dd, *J* = 9.8, 4.9, 1H) 3.40 (dd, *J* = 9.8, 6.2, 1H), 2.61 (m, 2H), 2.48 (m, 1H), 2.30 (m, 2H), 2.10 (m, 2H), 1.75−1.42 (m, 6H), 1.68 (d, *J* = 0.9, 3H), 1.56 (d, *J* = 3.4, 3H), 1.06 (m, 1H), 1.05 (s, 9H), 1.05 (s, 9H), 0.95 (d, *J* = 6.7, 3H), 0.90 (d, *J* = 6.6, 3H); ^{13}C NMR δ 151.5, 145.7, 136.1, 135.8, 135.7, 134.8, 134.7, 134.7, 134.2, 131.9, 130.6, 129.7, 129.6, 129.6, 129.6, 129.5, 127.7, 127.6, 127.6, 127.5, 127.4, 113.6, 104.5, 81.3, 78.5, 73.5, 70.1, 68.5, 42.4, 41.1, 40.2, 40.1, 33.7, 32.0, 30.9, 30.7, 27.2, 27.0, 21.0, 19.6, 19.5, 18.2, 17.8, 14.6; HRMS (ESI+) *m*/*z* calcd for $C_{59}H_{84}NO_4Si_2$ $(M + NH_4)^+$ 926.5933, found 926.5923.

(2*R*,5*S*)-Tetrahydro-5-[(1*E*,3*S*,6*E*,8*R*,10*R*)-bis[(3,11-*tert*-butyldiphenylsilyl)oxy]-5-methylene-6,8,10-trimethyl-1,6-un-

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decadienyl]-2-[(3*S*,5*E*)-3-[(*tert*-butyldiphenylsilyl)oxy]-5-heptenyl]-3-methylenefuran (11). To a stirred solution of **10** (0.049 g, 0.054 mmol) and imidazole (0.011 g, 0.16 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was added TBDPSCl (0.021 mL, 0.081 mmol) at rt. One hour later, the solvent was concentrated, and the residue was directly purified by flash chromatography (10% ethyl acetate in hexanes) to afford **11** in practically quantitative yield: R_f (10% EtOAc in hexanes) 0.90; ^{1}H NMR δ 7.71−7.63 (m, 12H), 7.36 (m, 18H), 5.55 (dd, J = 15.5, 7.1, 1H), 5.26 (m, 2H), 5.19 (dd, J = 15.5, 6.8, 1H), 5.04 (d, J = 9.5, 1H), 4.97 (d, J = 9.0, 1H, minor), 4.91 (d, J = 1.5, 1H, major), 4.88 (d, J = 1.5, 1H, minor), 4.82 (br s, 1H), 4.76 (br s, 1H, major), 4.73 (br s, 1H, minor), 4.61 (br s, 1H), 4.25 (q, J = 7.1, 1H), 4.09 (m, 1H), 4.01 (m, 1H), 3.71 (m, 1H), 3.44 (dd, J = 9.7, 4.7, 1H), 3.32 (dd, J = 9.8, 6.5, 1H), 2.62 (dd, J = 13.7, 6.1, 1H, minor), 2.55 (dd, J = 13.7, 6.8, 1H, major), 2.34 (m, 3H), 2.08 (m, 2H), 1.93 (m, 1H), 1.66−1.38 (m, 6H), 1.55 (s, 3H), 1.51 (s, 3H), 1.04 (m, 18H), 1.01 (m, 9H), 0.88 (d, J = 6.6, 3H, minor), 0.85 (d, J = 6.7, 3H, major), 0.75 (d, J = 6.5, 3H, major), 0.68 (d, J = 6.5, 3H, minor); ^{13}C NMR δ 151.8, 145.5, 136.1, 136.1, 136.1, 135.8, 135.7, 135.6, 135.5,134.8, 134.8, 134.6, 134.4, 134.4, 134.2, 134.2, 132.1, 130.3, 129.7, 129.6, 129.6, 129.5, 129.5, 127.7, 127.6, 127.5, 127.5, 127.5, 127.4, 127.4, 113.6, 104.1, 81.1, 78.3, 73.5, 73.0, 68.5, 43.3, 40.9, 40.1, 40.0, 33.6, 31.9, 30.9, 30.5, 27.2, 27.2, 27.0, 20.9, 19.5, 19.5, 18.2, 17.7, 14.4; HRMS (ESI+) m/z calcd for $C_{75}H_{102}NO_4Si_3$ $(M + NH_4)^+$ 1164.7111, found 1164.7116.

(2*R*,4*R*,5*E*,9*S*,10*E*)-9-[(*tert*-Butyldiphenylsilyl)oxy]-11-[(2*S*,5*R*)-tetrahydro-5-[(3*S*,5*E*)-3-[(*tert*-butyldiphenylsilyl)oxy]-5-heptenyl]-4-methylene-2-furanyl]]-2,4,6-trimethyl-7-methylene-5,9-undecadien-1-ol (12). To a solution of **11** (0.114 g, 0.099 mmol) in anhydrous THF (2 mL, 0.05 M) was added TBAF (tetrabutylammonium fluoride·3H_2O, 1 M in THF, 0.099 mL, 0.099 mmol) at 4 °C, and the reaction was stirred for 15 h. The mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography (10% to 30% ethyl acetate in hexanes) to obtain primary alcohol **12** (0.058 g, 64%, 98% brsm) as a colorless oil: R_f (10% EtOAc in hexanes) 0.20; ^{1}H NMR δ 7.66 (m, 8H), 7.36 (m, 12H), 5.57 (dd, J = 15.5, 7.2, 1H), 5.27 (m, 2H), 5.19 (dd, J = 15.5, 7.0, 1H), 5.06 (d, J = 9.3, 1H), 4.95 (d, J = 1.5, 1H, major), 4.92 (d, J = 1.5, 1H, minor), 4.82 (d, J = 1.5, 1H), 4.80 (br s, 1H, major), 4.72 (br s, 1H, minor), 4.62 (br s, 1H), 4.28 (q, J = 6.9, 1H), 4.12 (m, 1H), 4.04 (m, 1H), 3.70 (m, 1H), 3.43 (m, 1H), 3.30 (dd, J = 10.5, 6.6, 1H), 2.59 (m, 1H), 2.46 (m, 1H), 2.40 (m, 1H), 2.33 (m, 1H), 2.08 (m, 2H), 1.95 (m, 1H), 1.68−1.40 (m, 5H), 1.64 (s, 3H), 1.54 (d, J = 4.2, 3H), 1.15 (m, 1H), 1.04 (s, 9H), 1.02 (s, 9H), 0.88 (m, 1H), 0.81 (d, J = 6.8, 3H), 0.80 (d, J = 7.2, 3H); ^{13}C NMR δ 151.7, 145.5, 136.2, 136.1, 136.1, 135.8, 134.9, 134.8, 134.6, 134.4, 132.3, 130.5, 129.8, 129.7, 129.6, 129.5, 127.9, 129.6, 129.5, 127.9, 127.7, 127.6, 127.5, 127.4, 113.8, 104.2, 81.1, 78.4, 73.5, 73.0, 68.2, 43.3, 40.9, 40.2, 40.0, 33.6, 32.0, 31.0, 30.4, 27.2, 27.2, 20.8, 19.6, 19.5, 18.2, 17.2, 14.5; HRMS (ESI+) m/z calcd for $C_{59}H_{84}NO_4Si_2$ $(M + NH_4)^+$ 926.5933, found 926.5936. Once **11** and **12** were separated, the procedure was repeated (86% overall yield of **12**).

(2*R*,4*R*,5*E*,9*S*,10*E*)-9-[(*tert*-Butyldiphenylsilyl)oxy]-11-[(2*S*,5*R*)-tetrahydro-5-[(3*S*,5*E*)-3[(-*tert*-butyldiphenylsilyl)oxy]-5-heptenyl]-4-methylene-2-furanyl]]-2,4,6-trimethyl-7-methylene-5,9-undecadienoic Acid (13). To a stirred solution of alcohol **12** (0.093 g, 0.102 mmol) in CH_2Cl_2 (1 mL, 0.1 M) were added K_2CO_3 (0.057 g, 0.41 mmol) and DMP (Dess−Martin periodinane, 0.087 g, 0.206 mmol) at 0 °C, and the reaction was allowed to warm to rt and stirred for 1 h. It was quenched with aqueous sodium thiosulfate, extracted with dichloromethane, and dried over $MgSO_4$. The combined organic extracts were filtered and concentrated, and the residue was dissolved in H_2O/^{t}BuOH (1:1, 10 mL, 0.01 M) at 0 °C. To the solution mixture were sequentially added 2-methyl-2-butene (0.6 mL, 5.15 mmol), NaH_2PO_4 (0.16 g, 1.03 mmol), and $NaClO_2$ (0.047 g, 0.52 mmol). After 15 min, the reaction was warmed to room temperature. Two hours later, the reaction was diluted with H_2O (5 mL), and the aqueous layer was extracted with diethyl ether and ethyl acetate. The dried ($MgSO_4$) organic extracts were filtered and concentrated, and the residue purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to give **13** (0.051 g, 54% over two steps), as colorless oil: R_f (20% EtOAc in hexanes) 0.25; ^{1}H NMR δ 7.67 (m, 8H), 7.38 (m, 12H), 5.60 (dd, J = 15.5, 7.2, 1H), 5.26 (m, 3H), 4.97 (m, 2H), 4.85 (s, 1H), 4.82 (s, 1H), 4.64 (s, 1H), 4.28 (q, J = 6.8, 1H), 4.13 (m, 1H), 4.07 (m, 1H), 3.71 (m, 1H), 2.60 (dd, J = 13.7, 6.6, 1H), 2.51−2.24 (m, 4H), 2.10 (m, 2H), 1.97 (dd, J = 13.1, 10.4, 1H), 1.70−1.20 (m, 6H), 1.62 (s, 3H), 1.56 (d, J = 4.0, 3H), 1.07 (m, 12H), 1.04 (s, 9H), 0.83 (d, J = 6.5, 3H); ^{13}C NMR δ 182.3, 151.6, 145.4, 136.2, 136.1, 136.1, 134.8, 134.6, 134.4, 134.3, 133.5, 133.3, 130.4, 129.7, 129.6, 129.5, 127.6, 127.5, 127.5, 127.5, 127.4, 114.1, 104.2, 81.1, 78.4, 73.5, 73.0, 43.3, 41.3, 40.1, 40.0, 37.6, 31.9, 31.2, 30.9, 27.2, 27.1, 21.1, 19.5, 19.5, 18.2, 18.0, 14.6. HRMS (ESI−) m/z calcd for $C_{59}H_{77}O_5Si_2^-$ $(M - H)^-$ 921.5315, found 921.5324.

(2*R*,4*R*,5*E*,9*S*,10*E*)-9-[(*tert*-Butyldiphenylsilyl)oxy]-11-[(2*S*,5*R*)-tetrahydro-5-[(3*S*,5*E*)-3-hydroxy-5-heptenyl]-4-methylene-2-furanyl]]-2,4,6-trimethyl-7-methylene-5,9-undecadienoic Acid (14). To a stirred solution of carboxylic acid **13** (0.015 g, 0.016 mmol) in THF (0.05 mL) was added TBAF (0.3 mL, 0.3 mmol, 1 M in THF), and the reaction was warmed to 50 °C for 15 h. The solvent was removed, and the residue was purified by flash column chromatography (5% to 10% methanol in dichloromethane) to provide *seco*-acid **14** (7.0 mg, ca. 0.016 mmol, practically quantitative yield): R_f (10% methanol in dichloromethane) 0.5; ^{1}H NMR (500 MHz) δ 5.78−5.74 (m, 2H), 5.58−5.49 (m, 1H), 5.47−5.39 (m, 1H), 5.35 (d, J = 9.5, 1H), 5.10 (d, J = 1.5, 1H), 5.00 (br q, J = 1.7, 1H), 4.92 (br s, 1H), 4.83 (br m, 1H), 4.39−4.28 (m, 2H), 4.25 (m, 1H), 3.64 (m, 1H), 2.73−2.60 (m, 2H), 2.53 (dd, J = 13.9, 4.7, 1H), 2.47 (m, 2H), 2.41−2.33 (m, 1H), 2.16 (m, 2H), 1.86 (m, 1H), 1.79 (m, 1H), 1.76 (d, J = 1.1, 3H), 1.67 (dd, J = 6.2, 1.2, 3H), 1.67 (m, 2H), 1.53 (m, 1H), 1.41 (m, 1H), 1.16 (d, J = 7.0, 3H), 0.97 (d, J = 6.7, 3H); ^{13}C NMR (125.7 MHz) δ 179.9, 151.0, 146.1, 135.4, 133.8, 133.6, 130.6, 128.8, 127.3, 113.8, 105.0, 81.1, 78.8, 71.5, 70.7, 42.5, 41.4, 40.6, 40.0, 37.3, 32.2, 31.3, 31.0, 21.3, 18.2, 18.0, 14.8; HRMS (ESI−) m/z calcd for $C_{27}H_{41}O_5$ $(M - H)^-$ 445.2959, found 445.2969.

Compound 15 (10,11-Deepoxyamphidinolide K). To a stirred solution of 2-methyl-6-nitrobenzoic anhydride (MNBA, 6.7 mg, 0.019 mmol) and DMAP (6.9 mg, 0.056 mmol) in dichloromethane (6 mL) at room temperature was very slowly added, over 16 h, a solution of **14** (7.0 mg, 0.016 mmol) in CH_2Cl_2 (4 mL) using a mechanically driven syringe. One hour later, the resulting solution was washed with aqueous sodium hydrogen carbonate, dried, filtered, and concentrated to yield a crude product that was purified by flash column chromatography (2:1, hexanes/ethyl acetate) to afford **15** (5.0 mg, 71%) as a single stereoisomer (after separation from 10% of *epi*-**15**) as a colorless oil: R_f (33% EtOAc in hexanes) 0.4; ^{1}H NMR (500 MHz) δ 5.55 (m, 2H), 5.53−5.45 (m, 1H), 5.38−5.31 (m, 1H), 5.29 (d, J = 10.5, 1H), 5.05 (d, J = 1.5, 1H), 4.99−4.92 (m, 2H), 4.89 (br s, 1H), 4.87 (br q, J = 2.1, 1H), 4.43 (m, 1H), 4.30−4.25 (m, 1H), 4.25−4.19 (m, 1H), 2.88 (dd, J = 13.4, 4.9, 1H), 2.79 (ddt, J = 15.9, 7.5, 1.7, 1H), 2.75−2.67 (m, 1H), 2.48−2.37 (m, 2H), 2.36−2.26 (m, 2H), 2.17−2.09 (m, 1H), 1.82 (m, 2H), 1.72 (d, J = 1.1, 3H), 1.65 (dd, J = 6.4, 1.4, 3H), 1.62−1.53 (m, 3H), 1.28 (m, 1H), 1.13 (d, J = 7.1, 3H), 0.96 (d, J = 6.6, 3H); ^{13}C NMR (125.6 MHz) δ 176.1, 151.8, 145.5, 134.2, 133.8, 133.3, 133.3, 128.3, 126.2, 114.2, 104.9, 80.5, 78.5, 72.4, 71.8, 43.0, 41.0, 38.8, 37.4, 35.9, 31.5, 30.6, 29.9, 28.4, 21.0, 18.1, 18.0, 14.6; $[\alpha]_D$ = −15.4 ($CHCl_3$, c 0.18) [lit.[3] $[\alpha]_D$ = −10.4 ($CHCl_3$, c 0.08)]; HRMS (ESI+) m/z calcd for $C_{27}H_{41}O_4$ $(M + H)^+$ 429.2999, found 429.3006.

(−)-Amphidinolide K (1).[3] To a solution of L-(+)-diethyl tartrate (0.028 mL, 0.163 mmol) and titanium tetraisopropoxide (0.042 mL, 0.140 mmol) in anhydrous dichloromethane (1.25 mL) were added crushed molecular sieves (4 Å, 25 mg), and the suspension was stirred for 30 min at −20 °C.[3] *tert*-Butyl hydroperoxide (0.051 mL, 5.5 M in decane, 0.28 mmol) was added, and the mixture was stirred for further 30 min at −20 °C. The allylic alcohol **15** (4.30 mg, 0.0100 mmol) in dichloromethane (1.3 mL) was then added, and the mixture was stirred for 12 h at −20 °C. The reaction was quenched with water (0.1 mL) and filtered through Celite. The conversion was complete (by ^{1}H NMR). The concentrate was purified by flash column chromatography

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(20% ethyl acetate in hexanes) to afford **1** (4.0 mg, 90%) as a colorless oil: R_f (33% EtOAc in hexanes) 0.4; ^{1}H NMR (500 MHz, C_6D_6) δ 5.44−5.27 (m, 3H), 5.23 (m, 1H), 5.08 (d, J = 1.4, 1H), 4.92 (br s, 1H), 4.89 (br q, J = 2.1, 1H), 4.71 (br q, J = 2.1, 1H), 4.34 (t, J = 7.1, 1H), 4.15 (d, J = 8.5, 1H), 4.01 (td, J = 6.4, 1.6, 1H), 3.24 (dd, J = 13.5, 6.9, 1H), 3.18 (t, J = 2.4, 1H), 2.94 (m, 1H), 2.82 (t, J = 2.0, 1H), 2.53−2.49 (m, 2H), 2.44 (ddd, J = 11.4, 7.1, 4.2, 1H), 2.39−2.27 (m, 2H), 2.11 (dt, J = 13.0, 6.3, 1H), 1.93 (m, 1H), 1.83 (m, 2H), 1.53 (m, 2H), 1.80 (d, J = 1.0, 3H), 1.52 (d, J = 4.9, 3H) 1.10 (d, J = 7.1, 3H), 1.06−0.99 (m, 1H), 0.88 (d, J = 6.6, 3H); ^{13}C NMR (125.6 MHz, C_6D_6) δ 175.4, 151.5, 145.3, 134.5, 133.8, 127.0, 114.1, 104.2, 80.8, 74.3, 71.7, 65.7, 56.9, 56.0, 41.5, 40.0, 38.1, 36.1, 35.9, 31.0, 30.0, 29.2, 21.4, 19.3, 18.1, 14.6; $[\alpha]_D$ = −75 (MeOH, c 0.05) [lit.[1] $[\alpha]_D$ = −71 (MeOH, c 0.05); lit.[3] $[\alpha]_D$ = −75.2 (MeOH, c 0.06)]; HRMS (ESI+) calcd for $C_{27}H_{44}NO_5$ $(M + NH_4)^+$ 462.3214, found 462.3217.

In Vitro Experiments with Actin.[21] The effect of 40 mM solutions of each compound of Figure 1 on the polymerization of 10 mM G-actin was measured using a centrifugation method. Thus, 200 mL of G-buffer (2 mM Tris pH 8.0, 0.2 mM $CaCl_2$, supplemented with 2 mM $MgCl_2$, 100 mM KCl and 1 mM ATP) and 10 mM G-actin were incubated either with DMSO (vehicle), 40 mM solutions of the test compound, 40 mM solutions of phalloidin (an F-actin stabilizing agent), or 40 mM solutions of cytochalasin B (an inhibitor of F-actin polymerization) for 1 h at rt; at least two independent determinations were performed. After the incubation period, the samples were centrifuged at 100000g for 1 h in a TLA-100.2 rotor (Beckman). Supernatants were collected, and one volume of Laemmli buffer [62.5 mM Tris−HCl pH 6.8, 2% SDS (p/v), 5% 2-mercaptoethanol (v/v), 6 M urea and 0.05% bromophenol blue (p/v)] was added. Pellets were resuspended in 200 mL of SDS-NaPi buffer (10% SDS, 10 mM NaH_2PO_4), and the same volume of Laemmli buffer was added. Twenty milliliters of each sample (supernatant and pellet) was loaded in a 10% polyacrylamide gel; SDS-PAGE and a Coomassie brilliant blue staining and densitometry of actin bands were carried out. The mean values of densitometry were obtained for every duplicate.[22]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00966.

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Notes

The authors declare no competing financial interest.

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